LITERATURE CITED

1. A. I. Mikhalev, V. P. Chesnokov, and M. E. Konshin, Khim. Geterotsokl. Soedin., No. 6, 799 (1979).
2. A. I. Mikhalev and M. E. Konshkin, Khim. Geterotsikl. Soedin., No. 9, 1241 (1977).
3. N. I. Shramm and M. E. Konshin, Khim. Geterotsokl. Soedin., No. 5, 674 (1982).
4. S. Carboni, Gazz. Chim. Ital., 85, 1201 (1955).
5. A. Albert, in: Physical Methods in the Chemistry of Heterocyclic Compounds, Academic Press (1963).
6. A. Albert, R. Goldacre, and J. N. Phillips, J. Chem. Soc., No. 12, 2240 (1948).
7. A. Albert, J. Chem. Soc., No. 3, 1020 (1960).
8. L. Hammett, Physical Organic Chemistry, McGraw-Hill (1970).
9. K. D. Richie and U. F. Sedger, in: Modern Problems of Physical Organic Chemistry [Russian translation], Mir, Moscow (1967), p. 506.
10. B. Raymond and R. P. Mariella, J. Am. Chem. Soc., 69, 2670 (1947).
11. V. M. Petrichenko and M. E. Koshin, paper deposited at VINITI, No. 4947-81; Ref. Zh. Khim., 15Zh219 (1982).
12. L. A. Perez-Medina, R. P. Mariella, and S. M. McElvain, J. Am. Chem. Soc., 69, 2574 (1947)

SYNTHESIS AND LACTIM-LACTAM TAUTOMERISM OF 1,2-DIHYDROFURO[2,3-b]QUINOL-4-ONE DERIVATIVES

E. M. Peresleni, N. B. Marchenko, O. S. Anisimova, T. D. Kurochkina, V. G. Granik, and Yu. N. Sheinker

UDC 547.836.3:541.62:543.422'51

The reaction of O-ethylbutyrolactonium tetrafluoroborate with derivatives of ethyl anthranilate was used to synthesize tetrafluoroborates of cyclic imido esters, which were cyclized to furo[2,3-b]quinol-4-one derivatives by heating in a solution of sodium ethoxide. A number of N- and O-alkyl derivatives were obtained by alkylation of these compounds. The tautomerism of 6-chloro- and 7-chloro-2,3-dihydrofuro[2,3-b]quinol-4-ones that are unsubstituted in the benzene ring was studied, and a dependence of the position of the tautomeric equilibrium on the solvent and the substituent in the benzene ring was established.

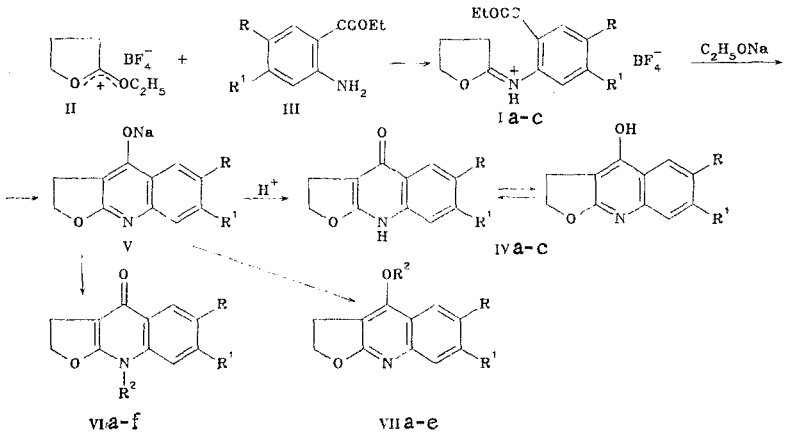
It has been previously shown [1] that imido ester salt Ia, obtained by the reaction of O-ethylbutyrolactonium tetrafluoroborate (II) with ethyl anthranilate (III), undergoes cyclization to 2,3-dihydrofuro[2,3-b]quinol-4-one (IVa) on treatment with sodium ethoxide. Salts Ib, c similarly undergo cyclization under the same conditions to furo[2,3-b]quinol-4-one derivatives (IVb, c). It was recently established [2] that substituted pyrrolino[2,3-b]quinol-4-ones are tautomeric compounds. One might have expected that replacement of the nitrogen atom in the five-membered ring by oxygen, as in the case of diazabicyclic systems [3], would promote a shift of the equilibrium to favor the lactim form. It therefore seemed of interest to study the corresponding analogs of pyrroloquinoline, viz., furo[2,3-b]quinolones (IVa-c).

For the investigation of tautomerism in this series of compounds it was necessary to synthesize their O- and N-alkyl derivatives, which could serve as models for the study of the tautomerism of IVa-c. The synthesis of such model compounds was realized by alkylation of the Na salts (V) of the furo[2,3-b]quinoline derivatives that are formed as intermediates in the cyclization of tetrafluoroborates Ia-c.

It should be noted that both N- and O-alkyl derivatives can be isolated from the resulting mixtures in the alkylation of salts V only in some cases (for example, for derivatives VIb and VIIa and the VId and VIIc isomeric pair). One isomer was isolated in the remaining cases, although it may be assumed from the mass-spectral data that both isomeric

S. Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry, Moscow 119815. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 376-381, March, 1984. Original article submitted October 17, 1983.

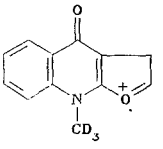
 0009-3122/84/2003-0304$08.50



I a R=R¹=H; b R=Cl, R¹=H; c R=H, R¹=Cl; IV a R=R¹=H; b R=Cl, R¹=H; c R=H, R¹=Cl; VI a R=R¹=H, R²=CH_3; b R=R¹=H, R²=CD_3; c R=H, R¹=Cl, R²=CH_3; d R=H, R¹=Cl, R²=$C_6H_5CH_2$; e R=Cl, R¹=H, R²=CH_3; f R=H, R¹=Cl, R²=$(CH_2)_2N(CH_3)_2$; VII a R=R¹=H, R²=CD_3; b R=R¹=H, R²=$CH_2C_6H_5$; c R=H, R¹=Cl, R²=$CH_2C_6H_5$; d R=Cl, R¹=H, R²=$CH_2C_6H_5$; e R=H, R¹=Cl, R²=$(CH_2)_3N(CH_3)_2$

compounds, one of which predominates (see below), are also formed by alkylation in these cases also. The initial task was to establish the structures of the compounds obtained, i.e., to ascertain the center (N or O) at which alkylation takes place. The positions of the substituents in the investigated VI and VII were established from the IR, UV, and mass spectra.

An examination of the electron-impact mass spectra of pairs of isomers (VIb and VIIa and VId and VIIc) make it possible to ascertian the characteristic peculiarities of the fragmentation of the N- and O-alkyl derivatives. Thus the presence in the spectrum of VIb of peaks of $[M - CO]^+$, $[M - CO - CH_3]^+$, and $[M - CO - HCO]^+$ ions (Table 1), which are due to elimination of the carbonyl group from the quinolone structure, indicates that the CD_3 group is attached to the nitrogen atom. A characteristic feature of the fragmentation of VIb is also the presence in the spectrum of a maximally intense $[M - H]^+$ ion, which is evidently associated with elimination of the hydrogen atom in the 2 position with subsequent stabilization of the charge on the ring oxygen atom:



Peaks of $[M - OCD_3]^+$ (170) and $[M - CD_3]^+$ (186) ions are observed in the spectrum of isomeric VIIa; a peak of the $[M - CO]^+$ ion is absent, and the peaks of $[M - H]^+$ and $[M - CO - HCO]^+$ ions have considerably lower intensities (Table 1). All of this indicates that VIIa is the trideuteromethoxy derivative. It follows from a comparison of the spectra of alkyl derivatives VIa, c, e with the spectra of isomers VIb and VIIa that the methyl group in these compounds is attached to the nitrogen atom. This is indicated by the presence in the spectra of intense $[M - H]^+$, $[M - CO - HCO]^+$, and $[M - CO]^+$ ions.* The lower relative intensity of the $[M - CO - HCO]^+$ peaks in the spectra of VIc, e as compared with the spectra of VIa, b can be explained by partial redistribution of the intensities of the peaks because of the introduction of a chlorine atom into the benzene ring.

A comparison of the spectra of VId and VIIc makes it possible to conclude that the former is the N-benzyl derivative and that the latter is the O-benzyl derivative. This is indicated by the intensities of the peaks of the $[M - H]^+$ ions (72% for VId and 12% for VIIc) and by the presence of intense peaks of $[M - C_6H_5]^+$ (234) and $[M - NHCH_2C_6H_5]^+$ (205) ions in the spectrum of VId and peaks of $[M - CH_2C_6H_5]^+$ (220) and $[M - OCH_2C_6H_5]^+$ (204) ions in the spectrum of VIIc. The spectra of benzyl devivatives VIIb, d do not contain peaks of $[M - H]^+$, $[M - C_6H_5]^+$, and $[M - NHCH_2C_6H_5]^+$ ions, and the spectra of these compounds are similar to the spectrum of benzyloxy derivatives VIIc; this makes it possible to assert that

*The spectra of VIa, c also contain low-intensity $[M - OCH_3]^+$ peaks, which indicates the presence of a small amount of admixed methoxy derivative in the samples.

TABLE 1. Peaks of the Characteristic Ions in the Mass Spectra of IV-VII[a]

Compound	m/z values (relative intensities in percent of the intensity of the molecular ion)							
	M	M−H	M−CO	M−CO−HCO	M−NHCH$_3$Ph	M−Ph	M−R$_2$	M−OR$_2$
IVa	187 (100)	186 (53)	159 (9)	130 (45)				170 (3)
IVb[b]	221 (100)	220 (55)	193 (8)	164 (23)				
IVc	221 (100)	220 (48)	193 (9)	164 (18)				
VIa	201 (100)	200 (91)	173 (7)	144 (36)			186 (5)	170 (3)
VIb	204 (100)	203 (100)	176 (10)	147 (50)				
VIc	235 (100)	234 (95)	207 (6)	178 (12)			220 (8)	204 (3)
VIe	311 (100)	310 (72)			205 (68)	234 (21)	220 (5)	
VIa	235 (100)	234 (91)	207 (8)	178 (15)			220 (6)	
VIIa	204 (100)	203 (35)		147 (7)			186 (10)	170 (16)
VIIb	277 (100)						186 (5)	170 (3)
VIIc	311 (100)	310 (12)			205 (14)	234 (4)	220 (14)	204 (8)
VIId	311 (100)				205 (4)		220 (4)	

[a]The maximum peak in the spectra of benzyl derivatives VId and VIIb-e is the peak of the benzyl cation (m/z 91). [b]Here and subsequently, the mass numbers and intensities of the ions that contain the ^{35}Cl isotope are presented.

the benzyl group in VIIb, d is attached to the oxygen atom.*

The N-alkyl and alkoxy derivatives have different spectra in the UV region. The most characteristic features of the O-alkyl derivatives are an absorption maximum at λ 260-280 nm (a minimum at λ 270 nm is observed in this region for the N-alkyl derivatives) and lower intensities of the long-wave maxima [for example, λ 332 nm (ε 5520) for VId and λ 311 nm (ε 26,600) for VId] (see Fig. 1). The spectra of these compounds remain virtually unchanged on passing from alcohol solutions to dioxane solutions. The IR spectra of the N-alkyl-substituted compounds differ from the IR spectra of the alkoxy compounds with respect to the presence of νCO and νC=C absorption bands at 1636-1663 cm^{-1} and 1555-1560 cm^{-1}, respectively, although the difference in the spectra in this region is small for VIa and VIIb (VIa: νCO 1636, νC=C 1623, 1587, 1555, and 1526 cm^{-1}; VIIb: νC=C 1623, 1579, 1510, and 1500 cm^{-1}); this hinders their use as model compounds for the determination of the structure of IVa. This fact, together with the relatively large widths of the bands in this region for IVa, complicates the selection of a hydroxy or oxo structure for it. However, the absence of a band at 1555 cm^{-1}, which is characteristic for the N-methyl model (VIa), makes it possible to assume that IV exists in the hydroxy form in the solid state. A higher νCO value (1659-1663 cm^{-1}) than in the case of VIa is observed in the spectra of the N-alkyl-substituted compounds that have a chlorine atom in the benzene ring (VIc-f); this facilitates the interpretation of the spectra of IVb, c. The IR spectrum of crystalline IVc does not contain the νCO and νC=C bands that are characteristic for the N-alkyl derivatives, but intense broad bands at 1628, 1570, and 1500 cm^{-1}, which are present in the spectra of model alkoxy compounds (for example, at 1625, 1576, and 1500 cm^{-1} for VIIc), are observed. The data obtained indicate that IVc has a hydroxy structure. A distinct band of stretching vibrations of a carbonyl group at 1659 cm^{-1} (at 1662 cm^{-1} for solutions† in $CHCl_3$) and νNH absorption at 2670-3150 cm^{-1} (at 3400 cm^{-1} in $CHCl_3$) are oberved in the IR spectrum of crystalline IVb. These data are in agreement with an oxo structure for IVb.

A lactim structure for IVa, c in the crystalline state is in agreement with the concept of a stronger shift of the tautomeric equilibrium to favor the hydroxy form in dihydrofuroquinolones as compared with pyrrolinoquinolones [3]. As regards IVb, its lactam structure is evidently due to the presence of a chlorine atom in the 6 position, which has an electron-acceptor effect on the hydroxy group of the lactim form and consequently increases its acidity. This effect determines the preponderance of the oxo form for IVb not only as compared with IVa but also as compared with the other chloro derivatives IVc, since the chlorine atom

*Peaks of $[M - H]^+$ and $[M - NHCH_2C_6H_5]^+$ ions, which indicate the presence of a small amount of admixed N-benzyl derivative in the sample, appear in the spectra at elevated temperatures in the case of fractionation of VIId by heating a sample in the direct-introduction system.

†We were unable to obtain the spectra of IVa, c in solutions in $CHCl_3$ in connection with their very low solubilities.

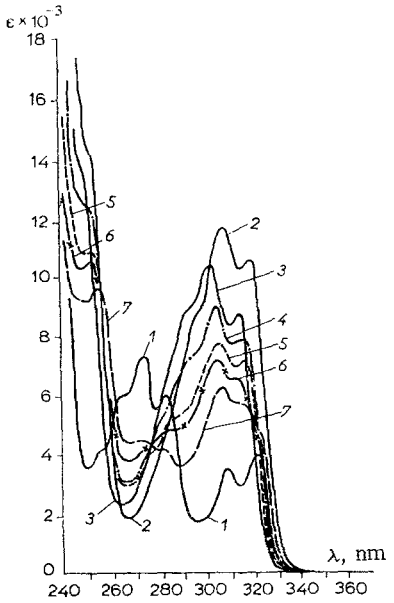
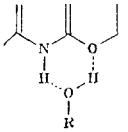


Fig. 1. UV spectra: 1) VIIb in alcohol; 2) VIa in alcohol; 3) IVa in alcohol; 4) IVa in alcohol with 50% dioxane; 5) IVa in alcohol with 75% dioxane; 6) IVa in alcohol with 90% dioxane; 7) IVa in dioxane.

in the latter is in the 7 position, and its electron-acceptor effect on the hydroxy group of the lactim form is smaller (for comparison, one may cite the pK_a values for m- and p-chlorobenzoic acids, which are, respectively, 3.83 and 3.98 [4]). It should also be pointed out that, on the other hand, a chlorine atom in the 7 position makes the NH group of the lactam form more acidic than a chlorine atom in the 6 position (compared, for example, the pK_a values of m- and p-chlorophenols, which are, respectively, 9.02 and 9.38 [5]). The combination of these effects should give rise to a tendency for an increase in the amount of the hydroxy form in equilibrium in IVc as compared with IVb.

All three compounds have the oxo structure in alcohol solutions; this follows from the similarity in their UV spectra and the spectra of the N-alkyl derivatives (an intense long-wave band at λ 300-320 nm and a minimum at λ 270-280 nm). The spectra of IVa, c undergo an appreciable change on passing from alcohol solutions to dioxane solutions: The intensity of the long-wave absorption (at 300-320 nm) decreases, and the absorption at 270-280 nm increases. The spectrum of IVb remains unchanged in this case, from which it may be concluded that for IVa, c the transition to dioxane solutions is accompanied by a shift in the equilibrium to favor the hydroxy form, whereas the lactam form remains the only form (within the limits of the sensitivity of the method) for IVb. A strong shift of the lactim-lactam equilibrium to favor the oxo form in hydroxy-containing solvents has been observed repeatedly for many similar tautomeric compounds and is evidently associated with the high energies of the hydrogen bonds formed by the lactam tautomers with such solvents.

In the examined compounds structures of the type



which, in addition to hydrogen bonds involving the C=O group, are also responsible for conversion of these substances to the lactam form in alcohol solutions, may be particularly favorable.

Hydrogen bonds of this type cannot be formed in dioxane solutions, and hydrogen bonds of the —OH···O< type become more favorable, and the lactim form becomes the preferred form. According to a rough estimate* from UV spectral data, the percentage of the lactim form amounts to 30-40% for IVa, c.

As we have already noted, the tautomeric equilibrium for furoquinolones IVa, c in the crystalline state is shifted to favor the hydroxy form to a considerably greater extent than in the case of pyrrolinoquinolones (VIII), which we investigated in [2]; this is in good

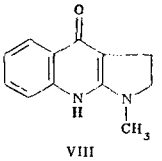
*The percentage of the hydroxy form was determined from the UV spectra as in [2].

TABLE 2. Characteristics of the Synthesized Compounds

Compound	mp, °C (solvent)	Reaction conditions	Found, %				Empirical formula	Calc., %				Yield, %
			C	H	Cl	N		C	H	Cl	N	
IVb	268—270[a]	See the exptl. section	59,7	3,7	16,1	6,5	$C_{11}H_8ClNO_2$	59,6	3,6	16,0	6,3	38
IVc	240—248[a]	The same	59,5	3,7	16,2	6,4	$C_{11}H_8ClNO_2$	59,6	3,6	16,0	6,3	55
VIb[b]	156—158[c]	20°, 1 h	—	—	—	6,6	$C_{12}H_8D_3NO_2$	—	—	—	6,9	69
VIc	228—230[d]	50—60°, 5 h	61,2	4,2	15,1	6,0	$C_{12}H_{10}ClNO_2$	61,1	4,3	15,1	5,9	11
VId	135—137[e]	See the exptl. section	69,0	4,4	10,8	4,4	$C_{18}H_{14}ClNO_2$	69,3	4,5	11,4	4,5	44
VIe	212—214[a]	20°, 5 h	61,3	4,1	14,6	6,1	$C_{12}H_{10}ClNO_2$	61,2	4,3	15,1	5,9	43
VIf	55—57[f]	50—60°, 5 h	61,5	5,6	11,5	9,5	$C_{15}H_{17}ClN_2O_2$	61,5	5,8	12,1	9,6	19
VIIag	138—140[d]	20°, 1 h	—	—	—	6,7	$C_{12}H_8D_3NO_2$	—	—	—	6,9	20
VIIb	180—181[d]	20°, 48 h	78,2	5,5	—	4,9	$C_{18}H_{15}NO_2$	78,0	5,4	—	5,1	63
VIIc	107—110[h]	See the exptl. section	69,4	5,0	11,3	4,7	$C_{18}H_{14}ClNO_2$	69,3	4,5	11,4	4,5	16
VIId	149—150[d]	60—70°, 5 h	69,5	4,3	11,0	4,4	$C_{18}H_{14}ClNO_2$	69,3	4,5	11,4	4,5	64
VIIe	128—130[e]	50—60°, 5 h	62,4	6,4	11,4	9,2	$C_{16}H_{19}ClN_2O_2$	62,6	6,2	11,6	9,1	24

[a]From DMF. [b]After the reagents were mixed, the mixture was warmed up to 50°C. [c]From 56% aqueous alcohol. [d]From ethyl acetate. [e]From isopropyl alcohol. [f]From petroleum ether. [g]Compounds VIb and VIIa were isolated in the same way as VId and VIIc (see the experimental sections). [h]From heptane.

agreement with the great electron-acceptor effect of the oxygen atom [3].



VIII

On the other hand, in solutions (dioxane or alcohol—dioxane solutions) the tautomeric equilibrium for VIII is shifted to favor the lactim form to a greater extent than for IVa, c (for example, 89% of the hydroxy form is present in dioxane in the case of VIII, as compared with 30-40% in the case of IVa, c). The observed effect can be explained by the presence of an N-methyl group in pyrroloquinoline VIII, which hinders solvation of the lactam form in dioxane and thereby promotes a greater shift of the equilibrium to favor the hydroxy form than in the case of IVa, c (see [2, 6] for a discussion of this sort of influence of steric effects on the position of tautomeric equilibria).

EXPERIMENTAL

The mass spectra were recorded with a Varian MAT-112 spectrometer with direct introduction of the samples into the ion source at an ionizing-electron energy of 70 eV and an ionization-chamber temperature of 180°C. The IR spectra of mineral oil suspensions were recorded with Perkin—Elmer 599 and 457 spectrometers. The UV spectra of solutions in alcohol, dioxane, and mixtures of dioxane with alcohol were obtained with a Perkin—Elmer 575 spectrophotometer. The synthesis of IVa and VIa was described in [1].

6-Chloro-2,3-dihydrofuro[2,3-b]quinol-4-one (IV). A 2-g sample of tetrafluoroborate II was added to a solution of 1.1 g of methyl 3-chloroanthranilate in 30 ml of anhydrous chloroform, and the mixture was stirred for 30 min. The chloroform was removed by distillation, the residue was triturated with ether, and the ether was decanted. An ether solution of triethylamine was added to the residue, the mixture was triturated, and the precipitate was removed by filtration. The ether filtrate was evaporated, and the residue was added in the course of 2.5 h to a solution of sodium ethoxide (from 0.5 g of Na and 30 g of absolute ethanol). The alcohol was removed by distillation, and the residue was dissolved in water. The aqueous solution was acidified to pH ∿ 7 with 2 N HCl solution, and the precipitate was removed by filtration and dried to give 0.5 g of IVb. Compound IVc was similarly obtained (see Table 2).

6-Chloro-9-benzyl-2,3-dihydrofuro[2,3-b]quinol-4-one (VId) and 4-Benzyloxy-6-chloro-2,3-dihydrofuro[2,3-b]quinoline (VIIc). Benzyl chloride (4 ml) was added to a suspension of 3 g (12 mmole) of sodium salt V in 40 ml of DMF, and the mixture was stirred at 60-70°C for 5 h. It was then evaporated in vacuo, and the residue was treated with water and extracted with chloroform. The extract was dried with sodium sulfate and filtered, and the chloroform was

evaporated. The residue was triturated with ethyl acetate and filtered to give 1.7 g (44%) of VId.

The ethyl acetate mother liquor was evaporated, and the residue was triturated with petroleum ether. The precipitate was removed by filtration and recrystallized from heptane to give 0.6 g (16%) of VIIc.

Compounds VIa-c, e, f, and VIIa, b, d, e were similarly obtained (see Table 2).

LITERATURE CITED

1. N. B. Marchenko and V. G. Granik, Khim. Geterotsikl. Soedin., No. 1, 65 (1982).
2. V. G. Granik, E. M. Peresleni, T. D. Kurochkina, A. M. Zhidkova, N. B. Marchenko, R. G. Glushkov, and Yu. N. Sheinker, Khim. Geterotsikl. Soedin., No. 3, 349 (1980).
3. L. N. Yakhontov, D. M. Krasnokut-skaya, E. M. Peresleni, Yu. N. Sheinker, and M. V. Rubtsov, Dokl. Akad. Nauk SSSR, 176, 613 (1967).
4. V. A. Palm, Introduction to Theoretical Organic Chemistry [in Russian], Vysshaya Shkola (1974), p. 242.
5. C. M. Judson and M. Kilpatrick, J. Am. Chem. Soc., 71, 3110 (1949).
6. L. N. Yakhontov, D. M. Krasnokutskaya, E. M. Peresleni, Yu. N. Sheinker, and M. V. Rubtsov, Dokl. Akad. Nauk SSSR, 172, 118 (1967).

STEREOCHEMISTRY OF NITROGEN HETEROCYCLES.

48.* SYNTHESIS, CONFIGURATIONS, AND IR SPECTRA OF 1,2-DIMETHYLDECAHYDROQUINOLINE-5-OL ISOMERS AND THEIR ACETATES

G. S. Litvinenko, N. Yu. Kuz'mina, and D. V. Sokolov

UDC 547.831.3.7.07:541.634:543.422

Three isomers of 1,2-dimethyldecahydroquinolin-5-ol and their acetates with cis and trans fusion of the rings and different orientations of the hydroxy and acyloxy groups were obtained. The correlation of the frequencies of the C–O, O–H, and N^+–H stretching vibrations with the configurations of these compounds was studied. The 1,2-dimethyl-cis-decahydroquinolin-5-ol isomer with a syn orientation of the amino and hydroxy groups exists in a conformation with an intramolecular hydrogen bond, the character of which is determined by the functional state of the amino group (OH...N in the base and N^+–H...O in the hydrochloride). The hydrochloride of the acetate of this alcohol does not form an intramolecular N^+–H...O($COCH_3$) bond.

We have previously obtained four isomeric 2-methyldecahydroquinolin-5-ols by hydrogenation of 2-methyl-5-keto-5,6,7,8-tetrahydroquinoline [2, 3]. Investigations of the chemical transformations and IR spectra made it possible to assign to three of these isomers 2α-methyl-trans-decahydroquinolin-5α-ol† (I), 2α-methyl-trans-decahydroquinolin-5β-ol (II), and 2α-methyl-cis-decahydroquinolin-5α-ol (conformation IIIA, with a syn orientation of the amino- and hydroxy groups and an intramolecular hydrogen bond) configurations.

In this paper we describe the synthesis of three isomeric 1,2-dimethyldecahydroquinolin-5-ols (IV-VI) and their acetates (VII-IX) and an investigation of their IR spectra in order to study the correlation between the three-dimensional structures of these compounds and their spectral characteristics.

*See [1] for Communication 47.

†The symbols α and β denote trans and cis orientations, respectively, of the substituent relative to 9-H.

Institute of Chemical Sciences, Academy of Sciences of the Kazakh SSR, Alma Ata 480100.

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 382-388, March, 1984. Original article submitted March 11, 1983.

0009-3122/84/2003-0309$08.50